REMARKS

Claims 1, 71-73, and 76-79 are pending in this patent application. Claims 1, 71-73, and 76-79 have been amended for consistency and to more clearly define the claimed invention. No claims have been added. Claims 74 and 75 have been canceled without prejudice or disclaimer. Support for claims 1, 71-73, and 76-79 as amended is found throughout the application as filed. Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

Claims 1 and 71 to 79 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Lee, et al., *Cell*, 1993, 75, 843-854 ("the Lee article"), Manche, et al., *Mol. Cell Biol.*, 1992, 12, 5238-5248 ("the Manche article"), published PCT application number WO 94/01550 ("the Agrawal application"), U.S. Patent Number 5,801,154 ("the Baracchini patent"), and U.S. Patent Number 5,519,134 ("the Acevedo patent"). Applicants respectfully request reconsideration and withdrawal of this rejection.

To establish *prima facie* obviousness, the Patent Office must identify "an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (emphasis added)(citing *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006).

The present rejection is not supported by a reason why one of skill in the art would have combined the teachings of the cited references to arrive at the present invention. To further establish facts concerning the cited art, applicants provide herewith the Declaration of David Corey, Ph.D. Dr. Corey, an expert in the field, explains the cited art and establishes, among other things, that there would have been no reason to combine the cited references to arrive at the present claims.

Independent claim 1 recites compositions comprising a duplex consisting of first and second chemically synthesized oligonucleotides that are not covalently linked to each other. Each of the oligonucleotides consists of 17 to 25 linked nucleosides, and the first oligonucleotide is 100% complementary to the second oligonucleotide and to a target mRNA; at least one of the

first and second oligonucleotides comprises a plurality of 2'-hydroxy-pentofuranosyl sugar moieties and each of the oligomeric compounds comprises a sugar surrogate. The cited references, when considered individually or in combination, fail to provide a reason for making such compounds.

The Lee article describes two endogenous transcripts encoded by the *C. elegans lin-4* gene: *lin-4*L, which is approximately 61 nucleotides in length and forms a stem-loop structure; and *lin-4*S, which is approximately 22 nucleotides in length and is identical to the first 22 nucleotides of *lin-4*L. See, e.g., the abstract and page 847, second column. These molecules are partially complementary to another *C. elegans* transcript, *lin-14*. The Lee article fails to describe or suggest duplexes comprising two separate, 100% complementary oligonucleotides each consisting of 17 to 25 linked nucleosides where one is 100% complementary to a target mRNA. See the Declaration of David Corey at paragraph 15. Moreover, since the molecules in the Lee article are endogenous transcripts, nothing in Lee suggests chemical modification of such oligonucleotides. See Declaration of David Corey, Ph.D., at paragraph 14.

The Manche article similarly fails to provide a reason to make the claimed oligonucleotides. See Declaration of David Corey, Ph.D., at paragraph 19. The article describes experiments for studying the interferon-induced protein kinase DAI using RNA duplexes consisting of pairs of oligonucleotides of 15, 23, 34, 40, 55, 67, 85, or 104 nucleosides. See, e.g., the abstract and figure 1. The duplexes that were 15 and 23 nucleotide pairs in length failed to elicit DAI activity and Manche speculates that duplexes shorter than 33 base pairs will not be active. Accordingly, there would be no reason to undertake further experiments with duplexes of oligonucleotides of the lengths claimed (17-25). See the Declaration of David Corey, Ph.D., at paragraph 16. Moreover, the Manche article provides no reason to use duplexes in which one oligonucleotide is complementary to a target mRNA or to incorporate modifications. See paragraphs 17 and 18.

The Agrawal application also fails provide a reason to make the claimed oligonucleotides. See Corey Declaration at paragraphs 25-28. Instead, the Agrawal application, e.g. at page 5, lines 13 – 17, describes single-stranded, self-hybridizing oligonucleotides useful for RNase H-based antisense. As explained in Dr. Corey's declaration at paragraphs 25 – 28, the Agrawal

application fails to describe or suggest complementary pairs of oligonucleotides consisting of first and second oligonucleotides that are not covalently linked to each other, as claimed.

The Baracchini patent likewise fails to provide a reason to make the claimed compounds, and thus fails to compensate for the deficiencies of the Lee and Manche articles and the Agrawal application. As Dr. Corey explains at paragraph 24 of his declaration, the Baracchini patent describes single-stranded RNase-H based antisense oligonucleotides. The Baracchini patent fails to teach or suggest duplexes of two separate 100% complementary oligonucleotides each consisting of 17 to 25 linked nucleosides, and thus fails to describe or suggest the claimed oligonucleotides.

Finally, the Acevedo patent also fails to provide a reason to make the claimed oligomeric compounds, and thus fails to compensate for the deficiencies of the Lee and Manche articles, the Agrawal application, and Baracchini patent. Instead, the Acevedo patent describes monomeric compounds that include a pyrrolidine moiety bearing a number of functional groups. See col. 6, lines 19 to 24. The monomeric compounds can be linked by certain of the functional groups to form oligomeric compounds. *Id.* Significantly, similar to the Baracchini patent, the Acevedo patent fails to teach or suggest *duplexes* of two 100% complementary oligomeric compounds 17 to 25 nucleosides in length, and thus fails to describe or suggest the claimed duplexes. See Declaration of David Corey, Ph.D., at paragraph 29.

Dr. Corey explains that none of the cited references individually -- nor all of them together -- provides a reason for making the claimed compounds. Without relying on the teaching in the present specification, which identifies a double-strand-specific RNase, the Office has not provided any reason for making the claimed compounds. Thus, the claimed subject matter would not have been obvious at the time of the invention. Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

Date: August 19, 2009

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